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Abstracts of the symposium ‘‘Raakvlakken tussen moleculaire genetica en kliniek’’¹

(Interfaces between molecular genetics and clinical practice)

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Early diagnosis of breast cancer in high risk women

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There is circumstantial evidence that population-based screening programmes for breast cancer can reduce mortality in women aged 50 to 70. However, the value of screening in younger women and/or in high-risk groups such as women with a positive family history of breast cancer is unproven. In the meantime a rapidly increasing number of high-risk women are seeking counselling about potentially preventive measures such as screening. As for ethical reasons no randomized trials are to be expected, the effect of screening of these women must be evaluated by means of observational studies. First results from a number of specialized centres are now appearing. In general, these studies describe the potential of screening to detect tumours in a relatively early stage with a malignancy potential that is lower than clinical cancers.

In the Rotterdam Cancer Institute a registration is being set up of high-risk women that are screened according to national guidelines, that include physical examination every six months and yearly mammography. Until date, 321 women were entered. Within a median follow-up time of 13.7 months, 5 tumours were detected.

These results suggest that selective screening of high-risk women might be effective. However, this conclusion is premature as, due to their observational character these studies might be subject to lead time, length and selection bias. While surrogate measures such as tumour stage may be useful as early indicators of the effect of screening, to date evidence on the ultimate endpoint, mortality, is lacking.

Measures of the effect of screening should include the extent of negative side effects such as the induction of tumours due to mammography and the detection of clinically insignificant cancers that would never have occurred in the absence of screening, as well as the impact on quality of life. Further, the cost-effectiveness of different screening procedures should be assessed. These uncertainties indicate the need of carefully designed, large, prospective studies with a complete and sufficient follow-up and a well-suited comparison group of unscreened women.

Magnetic resonance imaging of the breast

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In the short time MR imaging of the breast has been utilized for clinical imaging, this technique has proven to be a valuable tool, which is able to supply unique information about the nature of various breast lesions.

MR imaging will play an increasingly important role in the evaluation of breast disease and is at the moment used as an additional tool to the conventional imaging techniques.

With the by us used sequence, namely the TurboFLASH sequence, not only a high sensitivity (95%) has been reached, but also a high specificity (86%).

Indications for MR imaging are the following. MR imaging is important in the selection for breast saving therapy, because MR imaging shows much better the extent of a malignant lesion than mammography. Evaluation of women treated with silicone implants is difficult with mammography but with MR imaging the whole breast can easily be investigated.

Also women who are strongly suspected of having breast cancer or who are at high risk for developing breast cancer, but who have equivocal mammographies due to very dense glandular tissue, will benefit from this technique.

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Until now breast studies have been performed using whole body systems with specially developed dedicated breast coils. The high costs of operating these machines and the limited availability prevent its use for breast imaging on a large scale, but with dedicated MR breast scanners easier accessibility and lower costs will be reached, so together with fast imaging sequences a high patient throughput becomes feasible.

Ataxia telangiectasia and high predisposition for cancer

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The autosomal recessive disease Ataxia Telangiectasia (A-T) has been associated with an extremely high predisposition for cancer (more than 100-fold increase) and a high sensitivity of ionizing radiation. Individuals that have inherited one mutated allele of the Ataxia Telangiectasia gene (ATM) are known to be radiation sensitive and have a 1.9-fold increased risk for developing cancer (relative risk for breast cancer 3.9-fold). It is thought that 0.5% of the western population is heterozygous for ATM, and that 8% of all cases of breast cancer before age 40 can be attributed to ATM heterozygosity.

Recently, the ATM gene has been cloned and we have developed a protein truncation test (PTT) for rapid screening of frame-shift mutations of the coding region of the gene. In a first series of experiments we have established the mutation spectrum of ATM as present in Dutch Ataxia Telangiectasia patients. Fourteen different mutations in nine A-T patients have been identified using PTT that are scattered throughout the complete open reading frame. This indicates that there is no predominant Dutch ATM founder mutation, as is sometimes seen for other inherited (cancer) susceptibility genes.

Radiation exposure at young age is an established risk factor in development of breast cancer. Particularly, we have found that women treated for Hodgkin's disease before age 20 with mantle-field irradiation have a 40-fold increased risk of developing breast cancer within the next 10–20 years. Also, patients who received radiotherapy before age 40 for treatment of breast cancer have a 2–3-fold increased risk for developing contralateral breast cancer within the next 10–20 years. The frequency of ATM heterozygosity in these patient groups will be compared with the frequency in women that have been treated similarly and did not develop breast cancer. Thus, we can test the hypothesis that ATM heterozygous women have a disproportional high risk for developing radiation-induced breast cancer.

Clinical and genetic evaluation of ovarian cancer families

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The purpose of the study was to determine the prevalence of BRCA1 and BRCA2 germline mutations among patients from ovarian cancer families and to evaluate age at diagnosis, histology and FIGO stage in the study group.

We reviewed 50 ovarian cancer patients from 30 ovarian cancer families. The 30 ovarian cancer families were subdivided into four groups based on the tumour type encountered and the pattern of disease in the family. (1) *Hereditary breast and ovarian cancer (HBOC)* and (2) *hereditary ovarian cancer (HOC)* were diagnosed when: (a) in the case of maternal transmission, at least three family members from two successive generations had a confirmed diagnosis of breast or ovarian cancer (or ovarian cancer only in HOC) in successive generations, one case being a first-degree relative of the other two cases, or (b) in case of paternal transmission, at least two first-degree relatives and one (paternal) second-degree family member from two successive generations had confirmed breast or ovarian cancer (or ovarian cancer only in HOC), in successive generations, (3) *familial breast and ovarian cancer (FBOC)* and (4) *familial ovarian cancer (FOC)* were diagnosed in the event of familial clustering of these tumour types if the pedigree data did not fulfill the criteria for either HBOC or HOC.

We compared relevant clinical characteristics with those of a cancer registry group. BRCA1 (exons 2–24) and BRCA2 (exon 11) germline mutation detection was performed by a protein truncation test and sequencing of BRCA1 exon 2 (185delAG mutation).

Ten (40%) of 25 families tested revealed a germline BRCA1 or BRCA2 mutation. Mutations were detected in 6 of 12 (50%) HBOC families in 3 or 8 (38%) of FBOC, and 1 of 5 (20%) of FOC families. Patients with ovarian cancer from the study group had significantly lower age at diagnosis with a mean age of 54.3 (range 31–77) compared to 62.4 (range 14–98) in the cancer registry group. In the study group a significantly higher proportion of patients was diagnosed with an advanced (III or IV) FIGO stage. Finally the study group showed a relatively high frequency of serous adenocarcinoma.

Prognosis of patients with hereditary non-polyposis colorectal cancer as compared to patients from the general population

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Several investigators have suggested a favorable survival for patients with Hereditary Non-Polyposis Colorectal Cancer